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Case Report with Review of Literature

Paraneoplastic Syndrome: A Missed Diagnosis

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Abstract

Paraneoplastic syndrome can involve a single organ or diverse organ systems. It is one of the rare manifestations of occult malignancy. A 47-year-old female patient with history of recent suspected herpes infection presented with features of extensive skin darkening and thickening, associated with poor swallowing and cough reflex. Patient was not able to lift both arms nor able to sit or stand which was suggestive of proximal muscle weakness involving the shoulders and hip. Patient's initial workup for autoimmune disorders including dermatomyositis was negative. With paraneoplastic syndrome as differential diagnosis contrast-enhanced computed tomography chest and abdomen and tumor markers CA125 and CA19.9 done showed no evidence of occult malignancy. Patient was started on empirical steroids for polyradiculoneuropathy. After starting steroids patients was able to sit and walk with support. Patient was able to swallow liquids without aspiration. On regular follow-up over a period of 3 months, patient developed abdomen pain and abdominal distention which on evaluation showed ascites and multiple new cystic ovarian lesions suggestive of ovarian malignancy. Patient's CA125 was repeated and was markedly elevated. Patient was referred to an oncologist and was started on chemotherapy along with immunosuppressants. This case report emphasizes the need for regular follow-up of patients suspected of paraneoplastic syndrome. Although the initial workup for malignancy did not give a clue, on periodic review we were able to make the primary diagnosis and start appropriate treatment and achieve a better patient survival.

Keywords

- paraneoplastic syndrome
- dermatomyositis
- ovarian malignancy
- polyradiculoneuropathy

Introduction

Paraneoplastic syndrome (PNS) is one of the rarest manifestations of occult malignancies. The global incidence of PNS is less than 0.01%.[1] It is caused by immune cross-reactivity between malignant cells and normal tissues or by secretion of peptides hormones or cytokines. The development of these disorders does not necessarily correlate with cancer stage or prognosis of the patient. The common malignancies associated with PNS are gynecological malignancies, breast carcinoma, lung carcinoma, and hematological carcinomas. PNSs caused by these tumors can manifest as neurological disorders like cerebral ataxia, cranial nerve lesions, and dermatological manifestations, for example, dermatomyositis, polymyositis, or any endocrine abnormality, for example, syndrome of inappropriate antidiuretic hormone secretion. Patient presenting with PNS as an initial manifestation for a malignancy can lead to tracing of an occult malignancy and hence an early treatment of carcinoma and better outcome.

Case Report

A 47-year-old premenopausal female patient presented with drooling of saliva, aspiration on swallowing even saliva, nasal twang, proximal muscle weakness of both upper and lower limbs, power 3/5, and difficulty in walking. These symptoms

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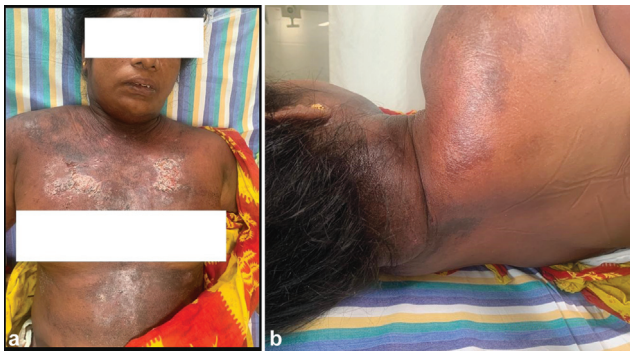

Fig. 1 (a, b) Dermatological manifestation presented as darkening and thickening of skin.

were preceded by extensive darkening and thickening of skin associated with itching on chest, shoulder, upper arm, and scalp regions (►**Figs. 1** and **2**). Patient had taken alternative treatment for 15 days and presented to us with the above symptoms. On examination the patient's Glasgow Coma Scale was 15, and was moving all four limbs. Neurological work up showed bilateral extensor plantar reflex and absent deep tendon reflex in both lower limbs which was suggestive of myelopathy and radiculopathy, respectively. Flaccid weakness of all four limbs including neck muscles was observed. Bilateral partial vagus nerve weakness and mild bilateral facial nerve weakness were also observed. Sensory perception was intact. Cerebrospinal fluid analysis was not done. Patient's erythrocyte sedimentation rate (ESR) and rheumatoid factor were normal. Her lactate dehydrogenase (LDH) was 935 IU/L (normal 105–233 U/L) and creatine phosphokinase (CPK) 266 U/L (normal 26–192 U/L). Autoimmune workup was done for skin lesions, which was all normal. Upper gastrointestinal (UGI) endoscopy done by a gastroenterologist for difficulty in swallowing showed normal UGI endoscopy till jejunum. Dermatologist opinion was obtained for skin lesions and empirical diagnosis of dermatomyositis, PNS, was made. With all the above findings and on suspicion of PNS, computed tomography (CT) of abdomen and chest was done to rule out occult malignancy which showed features of small right ovarian cystic lesion. Patient's CA125 was marginally elevated 65 U/mL (normal 0–35 U/mL). A premenopausal patient with a unilateral cystic lesion in ultrasound and CA125 valued at 65 U/mL, the patient's risk of malignancy index (RMI) when calculated was 65 (more than 200 high risk of malignancy) which was predictive of low risk of malignancy. Due to very low positive rate of PNS-related antibodies, paraneoplastic antibodies were not sent for analysis as per the request of the patient. As the RMI was low and predicted risk of malignancy was less the patient was initially started on pulse dose steroid (injection methylprednisolone 1 mg/kg/day). Patient's muscle weakness improved slowly and started mobilizing. Patient started swallowing liquids initially and her nasal twang improved. Patient was discharged on tapering dose of steroids with advice for regular follow-up. On regular follow-up, patient's muscle power and swallowing reflex improved slowly. On regular follow-up over a period of 3 months, patient complained of abdominal distention and pain. Ultrasound abdomen showed multiple cystic lesions in the right ovary associated with gross ascites and left pleural effusion. Her CA125 when repeated was more than 1,000 U/mL. Hence a diagnosis of CA ovary with PNS was confirmed and the patient was referred to an oncologist for further care. Patient's ascitic fluid was sent for analysis which showed multiple lymphocytes but no malignant cells. With the background of rapidly progressing symptoms and grossly elevated CA125, patient was started on chemotherapy for ovarian malignancy.

The uniqueness of this case is that PNS had involved multiple organ systems, the cranial nerves, muscles, and the skin. Although we had a differential diagnosis of PNS, we could not prove it during the first presentation as initial workup for malignancy showed low risk of malignancy.

Investigations

Complete blood count, renal function test, liver function test, serum electrolytes, ESR, C-reactive protein, LDH, and CPK.

Contrast-enhanced CT abdomen and chest, UGI endoscopy, indirect laryngoscopy, autoimmune profile, ANA ds DNA, RO, LA ANTIBODIES SM, SS-B, SCL-70, NUCLEOSOME, HISTONE, AMA-M2 JO 1, n RNP, CA125, and CA19.9.

Treatment

Patient was treated with injection methylprednisolone 1 mg/kg/day (500 mg/day) and was switched to tablet prednisone starting with 40 mg/day with tapering dose on follow-up.

Outcome and Follow-up

Patient started mobilizing, and her swallowing and cough reflex improved. But dermatological lesions were resistant to treatment.

Discussion

PNSs present either as a single organ manifestation or multiple organ manifestation. Different PNSs can coexist in the same patient,[2] and this was illustrated in the present case. In the patient PNS presented both as a dermatomyositis and as polyradiculoneuropathy. Around two-thirds of patients suspected of having PNS have neurological symptoms, but no features of cancer at the time of presentation. Ovarian tumors account for about 10% of malignancies associated with PNS.[3] Paraneoplastic cerebellar degeneration is the most common paraneoplastic neurological syndrome, and may coexist with ovarian carcinoma.[4] Paraneoplastic neurological syndromes associated with ovarian tumors may also appear as a peripheral polyneuropathy with diffuse

paresthesia and anesthesia.[5] Ovarian teratoma in young females can present with encephalitis that manifests as psychosis, memory loss, and behavior disorder. They can also progress into seizures, dyskinesias, and autonomic instability.[6–8] Few other classic PNSs associated with ovarian malignancy are dermatomyositis, Lambert–Eaton myasthenic syndrome, opsoclonus, and myoclonus. It has been studied that on an average, patient present with neurological symptoms as a paraneoplastic manifestation approximately 6 months before the diagnosis of cancer. Although the presence of PNS-related antibodies is highly suggestive of the presence of tumors, the positivity rate is less than 1%. Therefore, even if the test is negative, the patient should be retested at 3 and 6 months for occult malignancy. In addition, the European Federation of Neurological Societies Task Force recommends periodic searches every 6 months for 4 years.[8] In a study conducted by Candler et al[9] also found a female preponderance of PNS. Beyond treatment of the underlying tumor, immune modulation is a key component of PNS therapy. Specific modalities of treatment include corticosteroids, corticosteroid-sparing agents (e.g., azathioprine, cyclophosphamide), anti-CD20 monoclonal antibody rituximab, intravenous immunoglobulin, and plasmapheresis (plasma exchange). The impact of PNS on overall prognosis is complex and reflects a number of factors. Development of a PNS may result in diagnosis and treatment of a cancer at an otherwise clinically occult and highly treatable stage. Delay in diagnosis due to unpresented malignancy and the rare nature of the disease lead to lots of apprehension from both patient and caretaker. Conversely, independent of the underlying malignancy, the PNS itself can result in substantial morbidity. Because PNS may cause irreversible pathological changes to the nervous system, treatment often results in symptom stability rather than improvement. Our patient had symptomatic improvement of neurological manifestation with steroids and her malignancy symptoms responded to chemotherapy.

Limitation

Paraneoplastic antibodies analysis and positron emission tomography scan could not be done.

Conclusion

When routine clinical examinations and complete relevant investigation fail to fetch the diagnosis we should be more suspicious on occult malignancy. Occult malignancy in the form of PNS should be kept in mind if the puzzles do not follow a fixed pattern. To bring PNS and occult malignancy to limelight, it is essential to have a frequent and regular follow-up of patient to initiate the definitive treatment at the earliest.

Learning Points

- Paraneoplastic neurological syndromes (PNS) are an indirect manifestation of malignancy and are mostly, if not entirely, a consequence of cross-reactivity between tumor and host antigens.
- Different PNS affecting various organ systems can occur in the same patient.
- Recognition of PNS is difficult, as it is not a common scenario and various symptoms can coexist together.
- Regular follow-up of patients to start early treatment for malignancy.

Patient Consent

Yes.

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None.

Conflict of Interest

None declared.

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